

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| In re Application of: |) | |
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| D'AMATO ET AL. |) | |
| G : 131 00/500 (50 |) | Examiner: B. Badio, Ph.D. |
| Serial No.: 09/780,650 |) | Art Unit: 1616 |
| Filed: February 12, 2001 |) | Aut Cint. 1010 |
| |) | |
| For: ESTROGENIC COMPOUNDS AS |) | |
| ANTI-MITOTIC AGENTS |) | |

SUBMISSION OF ART

Assistant Commissioner for Patents P.O. Box, 1450 Alexandria, VA 22313-1450

Sir:

Applicants submit herewith copies of various printed publications in support of the referenced application. The documents are itemized below.

Applicants respectfully submit that these printed publications show that the diseases that appear in Table 1 of the present specification were known by those skilled in the art to be associated with and/or mediated by angiogenesis. Therefore, a person skilled in the art would appreciate that a composition that inhibited angiogenesis could be used to treat any of the diseases disclosed in these printed publications to be associated with and/or mediated by angiogenesis.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 223/3-1450, an July 28, 2003.

Robert E. Richards - Reg. No. 29,105

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Foreign Patent Documents:

PCT/US90/02673 (WO90/15816) PCT/US91/00218 (WO 91/10424) EP 0 325 199 A2 (89100714.8)

Journals:

Aguayo et al., "Angiogenesis in acute and chronic leukemias and myelodysplastic syndromes", Blood, 2000 Sep 15;96(6):2240-2245.

Akova et al., "Optic disk neovascularization in a patient with cytomegalovirus retinitis associated with renal transplantation", Ocul Immunol Inflamm, 2000 Mar;8(1):63-65 (Abstract)

Almeida et al., "The distribution of LH39 basement membrane epitope in the tumour stroma of oral squamous cell carcinoma", J Pathol, 1992 April, 166(4):369-374

Anderson et al., "Multiple Myeloma: New insights and therapeutic approaches", Hematology (Am Soc Hematol Educ Program), 2000: 147-165 (Abstract)

Armstrong et al., "Detection of vascular endothelial growth factor and tumor necrosis factor alpha in epiretinal membranes of proliferative diabetic retinopathy, proliferative vitreoretinopathy and macular pucker", Ophthalmologica 1998;212(6):410-4 (Abstract)

Arnold et al., "Angiogenesis in wound healing", Pharmacol, 1991 Dec., 52(3):407-422

Azuma H, "Genetic and molecular pathogenesis of hereditary hemorrhagic telangiectasia" J Med Invest. 2000 Aug;47(3-4):81-90 (Abstract)

Bacharach et al., "In vivo patterns of expression of urokinase and its inhibitor PAI-1 suggest a concerted role in regulating physiological angiogenesis", Proc Natl Acad Sci USA, 1992 Nov 15, 89(22):10686-90 (Abstract)

Barczyk et al., "Mast cells in the gastrointestinal tract", Rocz Akad Med Bialymst, 1995; 40(1):36-57 (Abstract)

Baer et al., "Corneal laser photocoagulation for treatment of neovascularization. Efficacy of 577 nm yellow dye laser", Ophthalmology, 1992 Feb; 99(2):173-9 (Abstract)

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Bhooma et al., "Eales' disease: accumulation of reactive oxygen intermediates and lipid peroxides and decrease of antioxidants causing inflammation, neovascularization and retinal damage", Curr Eye Res, 1997 Feb;16(2):91-5 (Abstract)

Bisell et al., "Putting Tumours in Context", Nature Reviews/Cancer, 2001 Oct, (1): 46-54

Boehme et al., "Juxtapapillary choroidal neovascular membrane in a patient with Paget's disease and lattice corneal dystrophy", Am Optom Assoc, 1989 Aug; 60(8):612-616 (Abstract)

Bortone et al., "Inflammatory response and angiogenesis after percutaneous transmyocardial laser revascularization", Ann Thorac Surg, 2000 Sep; 70(3): 1134-1138 (Abstract)

Chang et al., "Corneal neovascularization", Curr Opin Ophthalmol, 2001 Aug;12(4):242-249

Coll-Vinent et al., "Dynamic pattern of endothelial cell adhesion molecule expression in muscle and perineural vessels from patients with classic polyarteritis nodosa", Arthritis Rheum. 1998 Mar; 41(3):435-444 (Abstract)

Cursiefen et al., "Angiogenesis in corneal diseases: histopathologic evaluation of 254 human corneal buttons with neovascularization", Cornea, 1998 Nov; 17(6):611-613

D'Amore et al., "Mechanisms of angiogenesis", Annu Rev Physiol, 1987, 49:453-464

Danis et al., "Anti-angiogenic therapy of proliferative diabetic retinopathy", Expert Opin Pharmacother, 2001 Mar; 2(3): 395-407 (Abstract)

De Laey et al., "Hyperlipofuscinosis and subretinal fibrosis in Stargardt's disease", Retina, 1995; 15(5):399-406 (Abstract)

Di Girolamo et al., "Active matrilysin (MMP-7) in human pterygia: potential role in angiogenesis", Invest Ophthalmol Vis Sci, 2001 Aug;42(9):1963-8 (Abstract)

El-Assal et al., "Clinical significance of microvessel density and vascular endothelial growth factor expression in hepatocellular carcinoma and surrounding liver: possible involvement of vascular endothelial growth factor in the angiogenesis of cirrhotic liver", Hepatology, 1998 Jun; 27(6): 1554-1562 (Abstract)

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Fan et al., "Stimulation of angiogenesis by substance P and Interleukin-1 in the rate and its inhibition by NK_1 or interleukin-1 receptor antagonists", Br J Pharmacol , 1993 September, 110(1):43-9

Farmer et al., "Retinal vasculitis associated with autoantibodies to Sjogren's syndrome A antigen", Am J Ophthalmol, 1985 Dec 15;100(6):814-21; www.medterms.com "sicca syndrome" (Abstract)

Field, et al., "IMMUNOLOGY – Effect of thalidomide on the graft versus host reaction", Nature, 1966 Sept., 211(55): 1308-1310

Folkman et al., "Angiogenesis," J. Biol. Chem., 1992, 267(16): 10931-10934

Fregene et al., "Tumor-associated angiogenesis in prostate cancer", Anticancer Res, 1993 Nov-Dec, 13(6B):2377-2381

Gleichmann et al., "Immunoblastic lymphadenopathy, systemic lupus erythematosus, and related disorders. Possible pathogenetic pathways." Am J Clin Pathol, 1979 Oct;72(4 Suppl):708-723 (Abstract)

Griffioen et al, "Angiogenesis: potentials for pharmacologic intervention in the"&" treatment of cancer, cardiovascular diseases, and chronic inflammation", Pharmacol Rev 2000 Jun;52(2):237-268

Gutierrez-Rodriguez, "Thalidomide. A promising new treatment for rheumatoid arthritis", Arthritis Rheum., 1984, 27 (10):1118-1121 (Abstract)

Gutierrez-Rodriguez, et al., "Treatment of refractory rheumatoid arthritis—the thalidomide experience", J. Rheumatol., 1989, 16(2):158-163 (Abstract)

Handbook of Ocular Disease Management http://www.revoptom.com/handbook/hbhome.htm 2000-2001 Jobson Publishing LLC

Hajjar et al., "New concepts in fibrinolysis and angiogenesis", Curr Atheroscler Rep, 2000 Sep;2(5):417-21 (Abstract)

Hamanaka et al., "Retinal ischemia and angle neovascularization in proliferative diabetic retinopathy", Am J Ophthalmol, 2001 Nov;132(5):648-58 (Abstract)

Harada et al., "Angiogensis and vasodilation in skin warts" Association with HPV infection", Anticancer Res, 2000 Nov-Dec; 20(6B):4519-4523 (Abstract)

Application No. 09/780,650 Submission of Art in Support of Claims Page 5 of 10

Hattenbach et al., "Vitreous concentrations of TPA and plasminogen activator inhibitor are associated with VEGF in proliferative diabetic vitreoretinopathy", Retina, 1999;19(5):383-389 (Abstract)

Heney, et al., "Thalidomide treatment for chronic graft-versus-host disease", Br. J. Haematol., 1991, 78 (1):23-7

Hill et al., "Pathogenesis of pterygium", Eye, 1989;3 (Pt 2):218-226 (Abstract)

Hu et al., "Interleukin-8 stimulates angiogenesis in rats", Inflammation, 1993 April, 17(2):135-43

JR Jackson, MP Seed, CH Kircher, DA Willoughby and JD Winkler, "The codependence of angiogenesis and chronic inflammation", The FASEB Journal, Vol 11, 457-465

Jampol et al., "Peripheral proliferative retinopathies: an update on angiogenesis, etiologies and management", Surv Ophthalmol, 1994 May-Jun;38(6):519-540 (Abstract)

Kahlon et al., "Angiogenesis in atherosclerosis", Can J. Cardiol, 1992 Jan-Feb, 8(1):60-4 (Abstract)

Kalina et al., "Neovascularization of the disc in pars planitis", Retina, 1990, 10(4):269-73 (Abstract)

Keane et al., "The CXC chemokines, IL-8 and IP-10, regulate angiogenic activity in idiopathic pulmonary fibrosis", J Immunol 1997 Aug 1;159(3):1437-1443 (Abstract)

Kornmehl et al., "Bilateral keratitis in Lyme disease", Ophthalmology 1989 Aug; 96(8):1194-1197 (Abstract)

Landau et al., "Elevated levels of urokinase-type plasminogen activator and plasminogen activator inhibitor type-1 in malignant human brain tumors", Cancer Res 1994 Feb 15; 54(4):1105-1108 (Abstract)

Lee et al., "Ocular neovascularization: an epidemiologic review", Surv Ophthalmol 1998 Nov-Dec; 43(3):245-69

Lee et al., "Inhibition of growth and angiogenesis of human neurofibrosarcoma by heparin and hydrocortisone", J. Neurosurg, 1990 Sep., 73(3):429-435 (Abstract)

Application No. 09/780,650 Submission of Art in Support of Claims Page 6 of 10

Leveille et al., "Platelet-induced retinal neovascularization in leukemia", Am J Ophthalmol. 1981 May; 91(5):640-644, (Abstract)

Locci et al. "Angiogenesis: a new diagnostic aspect of obstetric and gynecologic echograph", J Perinat Med, 1994, 22:453-73

Logan, "Angiogenesis", Lancet, 1993 June 5, 341(8858):1467-8

MacLean et al., "Role of angiogenesis in benign, premalignant and malignant vulvar lesions", J Reprod Med, 2000 Aug; 45(8): 609-612 (Abstract)

Maddalozzo et al., "High angiogenic activity in cells isolated from cystic hygroma: role of bFGF", Arch Otolaryngol Head Neck Surg, 1999 Jan; 125(1):45-48 (Abstract)

Mahadevan et al., "Metastasis and angiogenesis", Acta Oncol, 1990, 29(1):97-103

Mann et al., "Choroidal neovascularization with granulomatous inflammation in ocular histoplasmosis syndrome", Am J Ophthalmol, 2000 Aug; 130(2):247-50 (Abstract)

Marti et al., "Hypoxia-induced vascular endothelial growth factor expression precedes neovascularization after cerebral ischemia", Am J Pathol, 2000 Mar; 156(3): 965-976 (Abstract)

Matsunaga et al., "Angiogenesis from the eighth cranial nerve to vestibular schwannomas", Acta Otolaryngol, 1996 Jan;116(1):52-8 (Abstract)

McCarthy et al., "Angiogenesis and the atherosclerotic carotid plaque: an association between symptomatology and plaque morphology", J Vasc Surg. 1999Aug; 30(2):261-8 (Abstract)

The Merck Manual of Diagnosis and Therapy, "Peripheral Ulcerative Keratitis", http://www.merck.com/pubs/mmanual/sections.htm Copyright © 1995-2001 Merck & Co., Inc., Whitehouse Station, NJ, USA. All rights reserved.

Mofidi et al., "Association between plaque instability, angiogenesis and symptomatic carotid occlusive disease", Br J Surg, 2001 Jul; 88(7):945-950 (Abstract)

Moulton et al., "Angiogenesis In The huPBL-SCID Model of Human Transplant Rejection", Transplantation 1999 Jun 27; 67(12):1626-1631

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Nelimarkka et al., "Decorin is produced by capillary endothelial cells in inflammation-associated angiogenesis", Am J Pathol 2001 Feb; 158(2):345-353 (Abstract)

Nelson JD, "Superior limbic keratoconjunctivitis (SLK), Eye, 1989;3 (Pt 2):180-189 (Abstract)

Paller et al., "Responses to anti-angiogenic therapies", J Investig Dermatol Symp Proc, 2000 Dec; 5(1):83-86 (Abstract)

Patz et al., "Clinical and experimental studies on retinal neovascularization", Am J Ophthalmol, 1982 Dec; 94(6):715-743 – XXXIX Edward Jackson Memorial Lecture (Abstract)

Penfold et al., "Age-related macular degeneration: ultrastructural studies of the relationship of leucocytes to angiogenesis", Graefes Arch Clin Exp Ophthalmol, 1987, 225(1):70-76 (Abstract)

Penn et al., "The effect of an angiostatic steroid on neovascularization in a rat model of retinopathy of prematurity", Invest Ophthalmol Vis Sci, 2001 Jan; 42 (1): 283-290 (Abstract)

Penn et al., "Variable oxygen exposure causes preretinal neovascularization", Invest Ophthalmol Vis Sci, 1993 March, 34(3):576-85

Potvin et al., "Mechanisms of action of antimalarials in inflammation: induction of apoptosis in human endothelial cells", J Immunol, 1997 Feb 15;158(4): 1872-1879 (Abstract)

Reddy et al., "Ocular complications of adult rheumatoid arthritis", Rheumatol Int 1996;16(2):49-52 (Abstract)

Ribatti et al., "Anti-angiogenesis: a multipurpose therapeutic tool", Int J Clin Lab Res, 1993, 23(3):117-120

Riono et al., "Scleritis: a clinicopathologic study of 55 cases", Ophthalmology, 1999 Jul;106(7):1328-1333 (Abstract)

Robinson et al., "Retinal vein occlusion", Am Fam Physician, 1992 Jun;45(6):2661-2666 (Abstract)

Rosen et al., "Regulation of angiogenesis by scatter factor", EXS, 1997;79:193-208 (Abstract)

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Roth et al., "Macular translocation for subfoveal choroidal neovascularization in angioid streaks", Am J Ophthalmol, 2001 Mar;131(3):390-392 (Abstract)

Rowsey et al., "Radial keratotomy: preliminary report of complications" Ophthalmic Surg, 1982 Jan;13(1):27-35 (Abstract)

Roy-Chaudhury et al., "Venous neointimal hyperplasia in polytetrafluoroethylene dialysis grafts", Kidney Int, 2001 Jun;59(6):2325-2334 (Abstract)

Sakaguchi et al., "Trehalose 6,6'-dimycolate (Cord factor) enhances neovascularization through vascular endothelial growth factor production by neutrophils and macrophages", Infect Immun, 2000 Apr; 68(4):2043-52

Sanislo et al., "Optic nerve head neovascularization in a patient with inactive cytomegalovirus retinitis and immune recovery", Am J Ophthalmol, 1998 Aug; 126(2):318-320 (Abstract)

Schaub et al., "Novel agents that promote bone regeneration", Curr Opin Biotechnol, 1991 Dec., 2(6):868-71 (Abstract)

Schweigerer et al., "Angiogenesis and Angiogenesis Inhibitors in Paediatric Diseases," Eur. J. Pediatr., 1992, 151:472-476

Servold, "Growth factor impact on wound healing", Clin Podiatr Med Surg, 1991 Oct., 8(4):937-53 (1991 Oct)

Sheela et al., "Angiogenic and invasive properties of neurofibroma Schwann cells", J Cell Biol, 1990 Aug;111(2):645-653 (Abstract)

Shweiki et al., "Patterns of expression of vascular endothelial growth factor (VEGF) and VEGF receptors in mice suggest a role in hormonally regulated angiogenesis", J Clin Invest, 1993 May, 91(5):2235-2243 (Abstract)

Strizzi et al., "Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma", J Patrol, 2001 Apr; 193(4); 468-475 (Abstract)

Sudhoff et al., "Angiogensis and angiogenic growth factors in middle ear cholesteatoma", Am J Otol, 2000 Nov; 21(6):793-798 (Abstract)

Sun et al., "In vivo and in vitro characteristics of interleukin 6-transfected B16 Melanoma Cells", Cancer Res 52(19):5412-5 (Oct. 1992)

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Tabbara, "Disruption of the choroidoretinal interface by toxoplasma", Eye, 1990; 4 (Pt 2):366-373 (Abstract)

Timar et al., "Angiogenesis-dependent diseases and angiogenesis therapy", Pathol Oncol Res, 2001;7(2):85-94 (Abstract)

Tuder et al., "The pathobiology of pulmonary hypertension. Endothelium", Chest Med, 2001 Sep; 22(3):405-418 (Abstract)

Vacca et al., "Angiogenesis in B cell lymphoproliferative diseases. Biological and clinical studies.", Leuk Lymphoma, 1995 Dec; 20(1-2):27-38 (Abstract)

Vadala et al., "Multifocal choroiditis: indocyanine green angiographic features", Ophthalmologica, 2001 Jan-Feb;215(1):16-21 (Abstract)

Walsh et al., "Angiogenesis in the pathogenesis of inflammatory joint and lung diseases", Arthritis Res, 2001;3(3): 147-153

Watson, "Management of Mooren's ulceration", Eye, 1997;11 (Pt 3):349-356 (Abstract)

Wiedemann, "Growth factors in retinal diseases: proliferative vitreoretinopathy, proliferative diabetic retinopathy, and retinal degeneration", Surv Ophthalmol, 1992 Mar-Apr; 36(5):373-84 (University Eye Clinic, Koln, Germany) (Abstract)

Yazaki et al., "Inhibition of angiogenesis and growth of human non-malignant and malignant meningiomas by TNP-470", J. Neurooncol, 1995, 23(1):23-29 (Abstract)

Zheng et al., "Control of stromal keratisis by inhibition of neovascularization", Am J Pathol, 2001 Sep; 159(3):1021-1029 (Abstract)

If the Examiner believes any informality remains in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is requested. No additional fees are believed due;

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however, the Commissioner is authorized to charge any deficiencies, or credit any overpayment to deposit account No. 11-0855.

Respectfully submitted

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Our File: 05213-0493 (43170-253692)